Bacterial Detection Testing by Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion

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Draft Guidance for Industry

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
December 2014

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Contains Nonbinding Recommendations

Draft – Not for Implementation

Bacterial Detection Testing by Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion

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Draft Guidance for Industry

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's or Agency's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

We, FDA, are issuing this guidance document to provide blood collection establishments and transfusion services with recommendations for initial testing (primary testing) for bacterial contamination of platelets intended for transfusion, and additional considerations for blood collection establishments and transfusion services for subsequent retesting (secondary testing) prior to transfusion. We are also proposing to allow the use of secondary testing of platelets as the basis to extend the dating period of platelets, when appropriately labeled bacterial detection devices and storage containers become available. Additionally, we are providing recommendations to licensed blood establishments for submitting Biologics License Application (BLA) supplements to include bacterial testing of platelet components. This guidance addresses all platelet products including platelets manufactured from Whole Blood (Whole Blood Derived (WBD) platelets), platelets collected by automated methods from a single donor (apheresis platelets), pooled platelets, and platelets stored in additive solutions[1]. The draft guidance, when finalized, is intended to supersede the recommendation in section VII.A.2, in regard to bacterial contamination testing in the document entitled "Guidance for Industry and FDA Review Staff: Collection of Platelets by Automated Methods" dated December 2007.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

[1] This draft guidance does not address the use of platelets processed with pathogen reduction devices. We recognize the potential for the future use of pathogen reduction technology in the United States (U.S.), and we may address the use of such devices in future versions of this guidance document.

II. BACKGROUND

Platelets are associated with a higher risk of sepsis and related fatality than any other transfusable blood component, and the risk of bacterial contamination of platelets stands out as a leading risk of infection from blood transfusion. This risk has persisted despite numerous interventions including the introduction, in the last decade, of analytically sensitive culture-based bacterial detection methods that are widely used to test platelets prior to their release from blood collection establishments to transfusion services (Ref. 1). We are issuing this guidance based on the knowledge we have gained over the past 14 years regulating bacterial detection devices and their use in blood establishments. See the Appendix to this document for more details on the background, history, and science of bacterial contamination of platelets.

III. CONSIDERATIONS FOR BACTERIAL TESTING OF PLATELETS BASED ON EVALUATION OF THE AVAILABLE SCIENTIFIC DATA

A. Sampling Volume and Culture Medium for Culture-Based Devices

Studies of culture-based devices that include aerobic and anaerobic media bottles labeled for use with 4-10 mL sampling volume have shown that sampling of an 8-10 mL volume into a single aerobic culture bottle would provide reasonable sensitivity for detection of the most clinically relevant organisms. This is based on a demonstration of comparable sensitivity, for clinically relevant organisms, of the 8 mL aerobic culture to a set of 4 mL aerobic and 4 mL anaerobic cultures (Refs. 2, 3, 4, 5). Superiority of a single 8 mL sample to a single 4 mL sample has been shown in multiple studies (Refs. 4, 5, 6). Larger sample volumes increase culture sensitivity, but are associated with higher rates of false positive cultures and additionally consume a larger proportion of the platelet product (Refs. 7, 8, 9, 10, 11). Clinical studies also have shown equivalent sensitivity of an alternative aerobic-only culture that samples a 3-4 mL volume per its instructions for use (Refs. 12 and 13).

Based on the information presented above, sampling the platelet product with the maximal volume permitted in the testing device instructions for use ($\pm$ sampling margin) and inoculating the volume into at least an aerobic culture medium is expected to achieve sensitivity comparable to that obtained by culturing 4 mL, each into an aerobic and an anaerobic culture. Though the incremental benefit of using an extra anaerobic bottle in detecting clinically relevant bacterial organisms is limited (Refs. 2, 8, 14, 15), we do not discourage the use of both an aerobic and an anaerobic bottle. We are not recommending a specific single maximal sample volume because the maxima may differ for different devices.

B. Rapid Testing of Platelets on Day 4 and Day 5

Considering the increased rates of transfusion-related septic reactions and fatalities associated with day 4 and day 5 platelet transfusions, and after considering the effect of performing a rapid bacterial detection test on the day of transfusion, the Blood Products Advisory Committee recommended testing of day 4 and day 5 platelets with a rapid test prior to transfusion even when a primary culture-based test was performed on day 1 (Refs. 10 and 16). When performed in accordance with the instructions for use of the FDA-cleared rapid bacterial detection devices, rapid testing of apheresis platelets is conducted within 24 hours prior to transfusion.

C. Considerations for Reassessing the Platelet Dating Period

1. Shortening of platelet dating

   Considering that 95 percent of platelet transfusion-related septic reactions and 100 percent of associated fatalities have occurred with day 4 and day 5 platelet transfusions, with almost even distribution between these two days, a shortening of platelet dating to 3 or 4 days could potentially reduce the rates of these adverse events (Ref. 17). However, it is acknowledged that assuring adequate platelet supplies in the relatively short interval during which platelets may be transfused under a 3 to 4 day dating period policy could be challenging for some transfusion services.

2. Extension of apheresis platelets dating for up to 7 Days

   According to 21 CFR 610.53(c), the dating period for platelets is *either* 72 hours from the time of collection of source blood, provided the labeling recommends storage at 20 to 24°C or between 1 and 6°C, *or* as specified in the instructions for use for the blood collection, processing, and storage system approved for such use by the Director, Center for Biologics Evaluation and Research (CBER). Supplies and reagents, including bacterial detection devices and platelet storage containers, must be used in a manner consistent with the manufacturer's instructions (21 CFR 606.65(c)).

IMPORTANT NOTE

Currently, appropriately labeled bacterial detection devices and platelet storage containers for the extension of dating beyond day 5 are not available. The additional considerations to extend platelet dating beyond day 5 (section VII.A.2 of this document) may not be implemented until the availability of both:

1) Bacterial detection devices cleared by FDA and labeled as a "safety measure[2];" **and**
2) Platelet storage containers cleared or approved by FDA for 7-day platelet storage and labeled with a requirement to test every product with a bacterial detection device cleared by FDA and labeled as a "safety measure."

In section VII of this document, FDA is providing additional considerations to extend the dating period for Platelets beyond 5 days and up to 7 days. Dating may be extended if: 1) the Platelets are collected in FDA-cleared 7-day platelet storage containers labeled with a requirement to test individual products with a bacterial detection device cleared by FDA and labeled for use as a "safety measure;" and 2) the Platelets are subsequently individually tested for bacterial detection using such a device, consistent with its instructions for use, and according to the following two strategies.

a. Extension of dating based on additional culture-based testing

Considering that transfusion-associated septic reactions and related fatalities rise on days 4 and 5 of storage, a repeat culture of the platelet product on the morning of day 4 or day 5 using a device cleared by FDA and labeled as a "safety measure," could be expected to identify contaminated units that were missed by the early culture and likely associated with organisms that have transitioned from the lag to the logarithmic growth phase (Ref. 14) late in storage. Such a repeat culture testing strategy could potentially allow for the safe extension of platelet dating for two additional days, up to 6 or 7 days, depending on when the repeat culture is conducted (day 4 or 5, respectively). This is analogous to the relative assurance of a day 1 culture which provides a 2-day relative safety period prior to the rise in the rate of septic reactions and related fatalities (Ref. 17).

[2] Note: FDA's current review practice is to permit labeling of tests for bacterial detection in platelets for transfusion as a "safety measure" when clinical studies have shown benefit for detection of contamination not revealed by previous bacterial testing and where clinical specificity was determined.

b. Extension of dating based on additional rapid testing

Consistent with the instructions for use of an FDA-cleared rapid bacterial detection device labeled as a "safety measure," the one-time use of a rapid test on day 5 or day 6 of storage could support a 24-hour dating extension after a negative test result, thereby extending the dating period through day 6 or day 7.

IV. PRIMARY AND SECONDARY TESTING OF PLATELETS

A. Primary Testing of Platelets

Primary testing of platelets is the initial/first time testing of a platelet component to detect the presence of bacterial contamination:

1. Early in storage, testing is conducted using culture-based or other equivalently sensitive tests.

2. When primary testing is performed proximate to issuance, a rapid bacterial detection device may be used consistent with its instructions for use.

B. Secondary Testing of Platelets

Secondary testing of platelets is any additional test of a platelet component to detect the presence of bacterial contamination in a unit that previously showed no bacterial contamination upon primary testing.

1. Secondary testing of platelets is usually conducted late in the storage period of platelet components and is intended to detect bacterial contamination not revealed by primary testing.

2. Secondary testing of platelets may be conducted with either a culture-based bacterial detection device or a rapid bacterial detection device, based on the needs of the blood establishment.

C. Secondary Testing of Platelets to Support Extension of Dating

Secondary testing of platelets for the purpose of extending the dating period of platelet components past a 5-day dating period should be conducted with a test labeled as a "safety measure," according to its instructions for use. Additionally, platelets should be stored in containers approved for extended storage periods.

V. FDA RECOMMENDATIONS FOR PRIMARY TESTING OF PLATELETS

Under 21 CFR 606.140(a), establishments must perform tests to assure that platelet components are safe, pure, potent and effective (*see also*, 21 CFR 211.165(a)). Accordingly, every transfusable platelet product should be tested at least once prior to transfusion with an FDA-cleared device intended for use in detecting bacteria in platelets for transfusion. The first test will be considered the primary test. We recommend that blood collection establishments have in place measures to promptly alert transfusion services in the event that a distributed platelet product is subsequently identified as positive for bacterial contamination.

NOTE: Day 1 of storage starts at midnight of the day of collection (*see also* 21 CFR 610.50(b) and 21 CFR 610.53(b)), and the product expiration time ends at midnight of the expiration date. Expiration is governed by the manufacturing processes, the labeling of the platelet storage container, and additional testing as described in this guidance.

A. FDA Recommendations to Blood Collection Establishments

1. Apheresis platelets

    a. Apheresis platelets should be tested using an FDA-cleared culture-based bacterial detection device no sooner than 24 hours after collection. To maximize the sensitivity of the culture, we recommend use of the maximal sample volume permitted by the device's instructions for use (+ sampling margin) and inoculation of the sample into at least an aerobic culture medium. If the blood collection establishment opts to sample a volume larger than the maximal inoculation volume described in the package insert, the amount of the sample that is in excess of the maximum volume recommended for use in the culture bottle should be used to inoculate additional bottles or pouches.

    b. We recommend that tested products be released to transfusion services under the following conditions:

        i. If the instructions for use of the bacterial detection device specify a minimal incubation period, release products consistent with the incubation period specified in the instructions for use of the bacterial detection device.

        ii. If the instructions for use of the bacterial detection device do not specify a minimal incubation period, release the products that have negative test results no earlier than 24 hours after culture inoculation. However, to ensure the availability of platelets, if you have measures in place to promptly alert the transfusion service that the product has tested positive for

bacterial contamination, you may release products that have negative test results no sooner than 12 hours after culture inoculation.

2. Pre-storage pooling

We recommend you test pre-storage pooled platelets using an FDA-cleared culture-based bacterial detection device no sooner than 24 hours after collection of the freshest unit in the pool, as per the pooling system instructions for use (Ref. 18). To maximize the sensitivity of the culture, we recommend use of the maximal sample volume permitted by the device's instructions for use (± sampling margin) and inoculation of the sample into at least an aerobic culture medium. If the blood collection establishment opts to sample a volume larger than the maximal inoculation volume described in the package insert, the amount of the sample that is in excess of the maximum volume recommended for use in the culture bottle should be used to inoculate additional bottles or pouches.

3. Single units of WBD platelets

For blood collection establishments that perform cultures on single units of WBD platelets, we recommend sampling, no sooner than 24 hours after collection, the largest feasible volume permitted by the FDA-cleared device's instructions for use (± sampling margin) and inoculation of the sample into at least an aerobic culture medium.

B. FDA Recommendations to Transfusion Services

1. Post-storage pooling

Transfusion services should perform an FDA-cleared rapid bacterial detection test within 4 hours of transfusion on pools of WBD platelets if the constituent single units were not previously tested.

2. Single units of WBD platelets intended for transfusion without prior pooling and not previously tested.

For single units of WBD platelets that are intended for transfusion without prior pooling (such as to the neonatal patient population) and that have not been previously tested, transfusion services should test according to either or both of the following strategies:

a. We recommend sampling, no sooner than 24 hours after collection, the largest feasible sample volume consistent with the FDA-cleared device's instructions for use (± sampling margin) and inoculation into at least an aerobic culture medium; and/or

b. We recommend using a rapid bacterial detection device cleared by FDA to detect the presence of bacteria in platelets for transfusion no sooner than 72 hours after collection. The product should be transfused within 4 hours of a negative rapid test result.

VI. ADDITIONAL CONSIDERATIONS FOR INVENTORY MANAGEMENT WITHOUT SECONDARY TESTING

In accordance with section III.C.1 of this document, transfusion services may also consider optimizing platelet inventory management to minimize, to the extent possible, the proportion of day 4 and day 5 platelets issued for transfusion.

VII. ADDITIONAL CONSIDERATIONS FOR SECONDARY TESTING OF PLATELETS (i.e., FOR PLATELETS WITH PREVIOUS PRIMARY TESTING FOR BACTERIAL CONTAMINATION)

A. Additional Considerations for Transfusion Services

In addition to implementing inventory management to minimize the proportion of day 4 and day 5 platelets issued for transfusion (section VI of this document), we suggest that transfusion services consider the following:

1. Implement secondary testing of apheresis platelets and pre-storage pooled platelets to enhance safety through day 5 storage as described below:

   a. On the day of transfusion, perform rapid testing on day 4 or day 5 platelets using a device cleared by FDA. Consistent with the instructions for use of the FDA-cleared device, rapid testing of apheresis platelets is conducted within 24 hours prior to transfusion;

   or,

   b. Culture on day 4, using a device cleared by FDA, for issuance 24 hours after the time of sampling on day 4, provided a negative result obtained.

2. Perform secondary testing of apheresis platelets or single units of WBD platelets, using a device cleared by FDA, to extend the dating period beyond day 5 and through day 6 or day 7, after registering as a manufacturer as described in section XI of this document.

IMPORTANT NOTE

Currently, appropriately labeled bacterial detection devices and platelet storage containers for the extension of dating beyond day 5 are not available. The additional considerations to extend platelet dating beyond day 5 in this section may not be implemented until the availability of both:

1) Bacterial detection devices cleared by FDA and labeled as a "safety measure;" **and**
2) Platelet storage containers cleared or approved by FDA for 7-day platelet storage and labeled with a requirement to test every product with a bacterial detection device cleared by FDA and labeled as a "safety measure."

a. Perform rapid testing, on the day of transfusion, on day 6 or day 7 platelets using a test cleared by FDA and labeled as a "safety measure." A negative rapid test result extends the dating period of the product for a period of 24 hours following the time of the test and not exceeding the 7-day expiration date of the product, *or*

b. Culture on day 4 using a test cleared by FDA and labeled as a "safety measure" for issue with a 48-hour extension (through day 6) following a negative result 24 hours after the time of day 4 sampling, *or*

c. Culture on day 5 using a test cleared by FDA and labeled as a "safety measure" for issue with a 48-hour extension (through day 7) following a negative result 24 hours after the time of day 5 sampling, *and*

d. See section XI of this document for registration requirements associated with extension of dating beyond day 5.

3. Transfusion services may opt not to conduct secondary testing.

B. Additional Considerations for Transfusion Services and Blood Collection Establishments

Platelet products that remain in the transfusion service inventory on day 4 and day 5 of storage may be shipped to cooperating collection establishments[3] for secondary rapid or culture testing. Testing and release of products may be conducted under the conditions set forth in section VII.A of this document. Blood collection establishments and transfusion services may opt not to conduct such secondary testing.

VIII. SUMMARY TABLE OF FDA RECOMMENDATIONS AND ADDITONAL CONSIDERATIONS

IMPORTANT NOTE

Currently, appropriately labeled bacterial detection devices and platelet storage containers for the extension of dating beyond day 5 are not available. The additional considerations to extend platelet dating beyond day 5 (section VII.A.2 of this document) may not be implemented until the availability of both:

1) Bacterial detection devices cleared by FDA and labeled as a "safety measure;" **and**
2) Platelet storage containers cleared or approved by FDA for 7-day platelet storage and labeled with a requirement to test every product with a bacterial detection device cleared by FDA and labeled as a "safety measure."

[3] Section 640.25(c) (21 CFR 640.25(c)) currently states that all manufacturing of platelets shall be performed at the same licensed establishment. FDA does not intend to take action to enforce this requirement.

Recommendations to Blood Collection Establishments	A. Apheresis and pre-storage pooled platelets: 1. Test using an FDA-cleared culture-based bacterial detection device no sooner than 24 hours after collection, and inoculate the sample into at least an aerobic culture medium. 2. Maximize the sensitivity of the primary culture by sampling the maximal volume permitted by the device's instructions for use. 3. If the instructions for use of the bacterial detection device specify a minimal incubation period, release products consistent with the incubation period specified in the instructions for use of the bacterial detection device. If the instructions for use of the bacterial device do not specify a minimal incubation period, release the products that have negative test results no earlier than 24 hours after culture inoculation. If the instructions for use of the bacterial detection device do not specify a minimal incubation period and you have in place measures to promptly alert the transfusion service that the product has tested positive for bacterial contamination, release products that have negative test results no earlier than 12 hours after culture inoculation. B. Single units of WBD platelets: If a blood collection establishment elects to test single units of WBD platelets, sample no sooner than 24 hours after collection the largest feasible volume permitted by FDA-cleared culture-based bacterial detection device into at least an aerobic culture medium.
Additional Considerations for Blood Collection Establishments	A. Platelet products that remain in the inventory of transfusion services on day 4 and day 5 may be shipped to cooperating blood collection establishments for secondary rapid or culture testing and re-issued to transfusion services. B. Blood collection establishments may opt not to perform such secondary testing.
Recommendations to Transfusion Services	A. Post-storage pools of WBD platelets if constituent single units were not previously tested: Test the platelet pool using an FDA-cleared rapid bacterial detection device within 4 hours prior to transfusion. B. Single units of WBD platelets not intended for pooling and not previously tested:

	1. Sample and test the unit no sooner than 24 hours after collection using the largest feasible volume permitted by FDA-cleared culture-based device into at least an aerobic culture medium; and/or 2. Use a rapid bacterial detection device cleared by FDA to detect the presence of bacteria in platelets for transfusion no sooner than 72 hours after collection. Transfuse within 4 hours of a negative test result.
Additional Considerations for Transfusion Services	A. Maximize, to the extent possible, inventory management by minimizing the proportion of day 4 and day 5 platelets issued for transfusion. B. Secondary testing of apheresis platelets and pre-storage pooled platelets to enhance safety through day 5: 1. Perform rapid testing on day of transfusion for day 4 or day 5 platelets; or 2. Perform culture on day 4 for release on day 5 after a negative result at least 24 hours after sampling. C. Secondary testing of apheresis platelets or single units of WBD platelets to extend the dating period through day 6 or day 7 upon availability of a) bacterial detection devices cleared by FDA and labeled as a "safety measure," and b) 7-day platelet storage containers labeled with a requirement to test every product with a bacterial detection device cleared by FDA and labeled as a "safety measure:" 1. Perform rapid testing on day of transfusion for day 6, or day 7 platelets; or 2. Perform culture on day 4 with a 48-hour extension through day 6 if negative result at least 24 hours after sampling; or 3. Perform culture on day 5 with a 48-hour extension through day 7 if negative result at least 24 hours after sampling. D. Platelet products that remain in inventory on day 4 and day 5 may be shipped to cooperating blood collection establishments for secondary rapid or culture testing and re-issued to transfusion services. E. Transfusion services may opt not to perform secondary testing on platelet products that remain in inventory on day 4 and day 5 or ship them to cooperating blood collection establishments for secondary testing, or to extend dating beyond day 5.

IX. LABELING

A. Labels on the Container

1. The container label

    a. The container labels must comply with 21 CFR 606.121 and 21 CFR 610.60. Blood collection establishments and transfusion services, as appropriate, must also follow the general requirements for labeling operations described in 21 CFR 606.120.

    b. The container labels must include the expiration date and time, if applicable, of the product based on bacterial detection testing (21 CFR 606.121(c)(4)(i)).

    c. If secondary testing is performed consistent with this guidance and the expiration date is extended to 6 or 7 days based on the bacterial testing performed, the blood establishment or transfusion service that performed the secondary testing must update the container label to reflect the new expiration date (21 CFR 606.121(c)(4)(i)).

2. A tie-tag

    a. Following secondary testing, we recommend that you attach a tie-tag to the platelet product to relay the following information:

        i. Type of bacterial detection test that was performed (rapid or culture test).

        ii. Date and time the bacterial detection test was performed.

        iii. The results of the bacterial detection testing.

    b. A single tie-tag may be attached to a pooled platelet product.

B. Circular of Information (21 CFR 606.122)

1. A circular of information must be available for distribution if the product is intended for transfusion (21 CFR 606.122).

2. We recommend that the circular of information inform the transfusion services that the platelet products have undergone primary bacterial detection testing. We recommend that the circular of information include the following statement:

"All apheresis and pre-storage pooled platelet products have been tested no earlier than 24 hours after collection using an FDA-cleared culture-based bacterial detection device."

3. The bacterial detection testing statement may be on a sticker or stamp that is applied to the inside or outside cover of the circular of information.

X. REPORTING IMPLEMENTATION FOR BACTERIAL DETECTION TESTING OF PLATELET PRODUCTS FOR LICENSED BLOOD ESTABLISHMENTS—REPORTING CHANGES TO AN APPROVED BIOLOGICS LICENSE APPLICATION (BLA)

An establishment that distributes platelet products in interstate commerce must have an approved BLA, in accordance with section 351 of the Public Health Service Act.

Licensed establishments must report changes to their approved BLAs in accordance with 21 CFR 601.12. The information below is intended to assist you in determining which reporting mechanism is appropriate for a change to your approved BLA, as it applies to the bacterial testing of platelet products and the manufacture of apheresis platelets and single units of WBD platelets with a 6 or 7-day dating period (or "expiration date"). You should prominently label each submission with the reporting category under which you are reporting your change, for example, "Prior Approval Supplement" or "Annual Report."

A. Prior Approval Supplement (PAS)

1. Changes requiring supplement submission and approval prior to distribution of the product made using the change (Major Changes) (21 CFR 601.12(b))

   Under 21 CFR 601.12(b), changes that have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product must be reported to FDA in a Prior Approval Supplement (PAS).

   Under this regulation, the following kinds of manufacturing changes would fall within this category, warranting submission of your request to implement the following changes to your approved BLA as a PAS:

   a. You do not currently hold an unsuspended, unrevoked BLA to manufacture apheresis, single WBD platelets, and pre-storage pooled WBD platelets and you would like to distribute these platelet products in interstate commerce.

b. You currently hold an unsuspended, unrevoked BLA to manufacture single WBD platelets and apheresis platelets with a 5-day expiration date and you choose to increase the storage time of single WBD platelets and apheresis platelet products to a 6-day or 7-day expiration date following secondary testing using collection and storage systems that are approved to store platelets more than 5 days and distribute these products in interstate commerce.

2. To comply with the requirements in 21 CFR 601.12(b)(3) and 601.12(f), the following should be included in your PAS.

   a. Identification of the components involved and manufacturing facility (facilities) and a detailed description of the manufacturing change (including name of device used for bacterial detection). We recommend that this information be documented in a cover letter and on the Form FDA 356h.

   b. Standard Operating Procedures (SOPs) – to allow us to assess the manufacturing change, we recommend that you include copies of the following procedures:

      i. Component manufacturing (if the SOPs were previously approved by FDA, include the reference number under which they were reviewed).

      ii. Bacterial detection testing, including when the platelet product is sampled and when the product will be released.[4]

      iii. Labeling the platelet product based on the results of the bacterial detection testing, including the timeframe after which the negative results are no longer valid.

      iv. Measures to promptly alert the transfusion service that product has tested positive for bacterial contamination.

      v. Quarantine and disposition of unsuitable products.

      vi. Investigation of units with positive test results.

      vii. Communicating to your consignees the type of storage container the platelets are stored in, for example, a storage container approved for 5-day storage or storage container

[4] You must perform the bacterial detection testing in a manner consistent with the manufacturer's instructions for use (21 CFR 606.65(e)).

approved for 7-day storage and when the bacterial detection testing was performed.

c. Labeling – include the following labeling in your supplement:

   i. Container labels: A container label for each platelet product, unless previously approved by FDA that includes the expiration date and time, if applicable, of the product based on bacterial detection testing.

   ii. Tie-Tag: An example of the tie-tag attached to each platelet product that will relay information about the secondary bacterial detection testing.

   iii. Circular of Information: A copy of the revised circular of information that informs the transfusion services that the platelet products have undergone primary bacterial detection testing.

d. The name, address and registration number, if available, of any contractors who are performing bacterial detection testing of platelet products for you.

e. Validation plan for the bacterial detection testing and a summary of the validation data.

f. Two consecutive months of quality control data for each product type you will be making (WBD platelets and apheresis platelets). Include a description of your sampling plan and the results for the following parameters:

   i. Results of all bacterial detection testing;

   ii. Residual white blood cell count;

   iii. Platelet yield; and

   iv. pH at expiration or issue.

B. Changes to be Described in an Annual Report (Minor Changes) (21 CFR 601.12(d))

Under 21 CFR 601.12(d), changes in the product, production process, quality controls, equipment, facilities, or responsible personnel that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product must be documented in an annual report submitted each year within 60 days of the anniversary date of approval of the application.

Under this regulation, the following kinds of manufacturing changes would fall within this category, warranting submission of the following changes to your approved BLA in your annual report noting the date the process was implemented:

1. You are a licensed blood collection establishment and you implement the bacterial detection testing as described in this guidance without modification and the expiration date of apheresis, single units of WBD platelets, and pre-storage pooled WBD platelets remains at 5 days.

2. You are a licensed blood collection establishment and either you or your contractor change from one type of FDA cleared bacterial detection device to another type of FDA-cleared bacterial detection device of the same methodology (culture or rapid method).

Note: For assistance in reporting your changes, see FDA's "Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture; Guidance for Industry" dated December 2014. The December 2014 guidance represents FDA's current thinking on this topic and can be found on FDA's website at: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm354559.htm.

XI. TRANSFUSION SERVICES—REGISTRATION AND BLOOD PRODUCT LISTING

All owners and operators of blood establishments that engage in the manufacture of blood products are required to register and list the blood products they manufacture, pursuant to section 510 of the Federal Food, Drug, and Cosmetic Act (21 CFR 607.7(a)). The implementation of a rapid or culture-based bacterial detection device that is used to re-label the platelet product with a 6 or 7-day expiration date is a manufacturing procedure requiring registration and blood product listing, as described in 21 CFR 607.3(d).

If you are a transfusion service that is currently exempt from registration and blood product listing under the provisions of 21 CFR 607.65(f) and you implement a rapid or culture-based bacterial detection test to determine the acceptability of platelet products to be released on day 6 or day 7 after collection, you must register your blood establishment with FDA and list the blood products you manufacture. We recommend that you note you are performing bacterial detection testing on platelet products in the "Other" field in the Products section.

Instructions on how to register electronically with FDA can be found on FDA's website at: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/EstablishmentRegistration/BloodEstablishmentRegistration/default.htm.

XII. IMPLEMENTATION

We recommend that you implement the recommendations contained in this guidance within 6 months after the final guidance is issued.

APPENDIX

I. CONTAMINATION OF PLATELETS WITH BACTERIA

All blood components are susceptible to bacterial contamination. Platelet components however are uniquely vulnerable to bacterial outgrowth because they are stored at room temperature (20°C-24°C). They can serve as a favorable medium for bacterial proliferation to high titers that may lead to sepsis and related fatality in patients transfused with contaminated platelet products.

Skin flora are the most common source of bacterial contamination. Contamination could also originate from asymptomatic occult donor bacteremia, or be introduced during processing of the platelet unit.

When bacteria are present, the bacterial load in the collection at sampling time is estimated to vary approximately between 1 and 65 colony forming units (CFU) per platelet storage container, which corresponds to a concentration ranging from less than 0.002 to 0.26 CFU/mL, depending on a collection volume range of 250 to 750 mL (Refs. 7, 8, 9, 19, 20, 21). For platelet components that become contaminated, a number of mechanisms may contribute to a low bacterial concentration at the time of sampling, which generally occurs no earlier than 18-24 hours post collection: 1) inactivation by antibacterial factors in plasma; 2) a prolonged lag phase of growth; 3) bacterial species that grow poorly in the aerobic conditions of platelet storage; 4) long generation time; 5) the existence of the bacteria as biofilms coating the container making them unavailable for sampling; and 6) phagocytosis of bacteria by white blood cells (Ref. 22). Thereafter, the initial bacterial load, if present, may follow one of several growth models: 1) it may become non-viable and die; 2) after a short lag phase, viable bacteria enter a logarithmic growth phase; 3) viable bacteria persist at low concentration in an extended lag phase before undergoing logarithmic growth; or 4) viable bacteria may simply persist at low concentrations throughout the platelet storage period (Ref. 22). Bacterial organisms have different generation (doubling) times; the generation time of most bacteria in platelets at 22°C varies between 1 and 4 hours with an average of approximately 2 hours for the most frequently encountered organisms (Ref. 23). Contaminating organisms may be fast or slow growers, Gram positive or Gram negative, aerobic or anaerobic, and may be more or less virulent (Refs. 2, 24, 25). The patient's susceptibility to bacteremia also varies, for example, with immune suppression and/or administration of antimicrobial therapy.

A number of strategies have been implemented in the U.S. to mitigate the risk of bacterial contamination of platelet products, including donor health screening to ensure that the donor is in good health at donation, skin disinfection, use of collection containers that divert the first 15-40 mL of the collection (an initial aliquot that is likely to contain the skin flora) away from the product, visual inspection of the platelet storage container for signs of gross contamination and the use of bacterial detection devices.

II. PLATELET COMPONENT USAGE AND PLATELET DATING PERIOD IN THE UNITED STATES

Approximately 2.2 million platelet transfusions are administered yearly in the U.S. (Ref. 26). Of those, about 91 percent are apheresis platelets and 9 percent are pools of WBD platelets, with each pool composed, on average, of 5 single units of WBD platelets. WBD platelets are pooled either within the 4 hours prior to transfusion (post-storage pooling), or pooled shortly after collection in a system cleared by FDA for extended storage of pooled platelets (pre-storage pooling).

Under 21 CFR 610.53(c), the dating period of platelets is *either* 72 hours from the time of collection, provided labeling recommends storage at 20°C to 24°C or between 1°C and 6°C, *or* as specified in the instructions for use for the blood collecting, processing, and storage system approved for such use by the Director, CBER. The current maximal dating period for platelets in the U.S. is 5 days.

In 2003, FDA approved a New Drug Application (NDA) Supplement for a storage system from a single manufacturer for the storage of single units of WBD platelets for up to 7 days with the requirement that the product must be tested for bacterial contamination using a bacterial detection system cleared by FDA for release of platelets for transfusion.

Thereafter, three additional platelet storage containers were cleared by FDA through the 510(k) regulatory pathway, for the storage of apheresis platelets for up to 7 days when the platelets are coupled with 100 percent screening for bacterial contamination using a device cleared by FDA for that purpose with its recommended methods prior to transfusion.

The 7-day dating period is not currently available for use because appropriate instructions for use for the platelet storage container and bacterial detection devices labeled to detect the presence of bacteria in platelets suspended in a liquid medium are not available for the extension of dating beyond day 5. However, once appropriately labeled bacterial detection devices are available they can be used in conjunction with 7-day platelet storage containers with appropriate instructions for use to extend the dating period to 7 days (please see section VII of this document)

III. METHODS TO DETECT BACTERIAL CONTAMINATION IN PLATELET COMPONENTS

Two main methodologies are used in the U.S. to detect bacteria in platelets: culture-based methods, which rely on the growth of bacterial organisms to levels detectable by the testing device; and rapid testing, which directly recognizes components of the bacterial organisms.

A. Culture-Based Devices

1. Current practices with culture-based devices

Culture-based devices have high analytical sensitivity (a low limit of detection) and an extensive record of clinical use in the U.S. since the devices were first cleared in 2002. They are traditionally used early in the storage of platelets. Currently available culture-based devices require the use of a significant sampling volume relative to the product, and they necessitate the concurrent use of equipment for incubation and detection.

Following the implementation in 2004 of an AABB Standard on testing platelets for bacterial contamination, culture-based devices have been used by most blood collection centers to routinely test virtually all apheresis platelet collections (Ref. 27). However, the exact sampling and culture practices by blood collection centers vary even in the use of a particular device (Ref. 28). Product sampling commonly occurs at least 18-24 hours after collection to allow for any organisms that are present to proliferate to levels that may be detectable by the device based on its sensitivity. Sampling is followed by a variable hold period prior to product release in order to permit time for adequate incubation of the culture.

Products tested by culture-based devices with continuous monitoring are distributed as "negative-to-date" based on the status of the culture at the time the unit is released to the transfusion service. The culture may turn positive after distribution of the unit, triggering notification of the transfusion service and product retrieval. Platelets tested using culture-based devices without continuous monitoring are released based on a single point-in-time measurement.

2. Rate of bacterial contamination following the use of a culture-based device

a. Apheresis products

The rate of bacterial contamination in apheresis platelets, as determined by sampling of platelets ≥ 24 hours after collection (commonly referred to as day 1 or early culture), varies between 1/2,836 and 1/8,431 based on confirmed culture results (Refs. 2, 3, 4, 7, 8, 12, 14, 29). However, studies have shown that a risk of bacterial contamination persists on the day of transfusion, or at outdate, in apheresis platelets that had tested negative by early culture, and that risk has been shown to vary between 1/1,500 – 1/2,747 (Refs. 3, 14, 30). The sensitivity of the early culture has been calculated to range between 11 percent and 47 percent; i.e.,

between 53 percent and 89 percent of bacterial contaminations of platelet products are missed by the early culture (Refs. 3 and 13). The residual risk of bacterial contamination has been shown to be mostly associated with slow-growing Gram positive organisms, providing evidence of the relative effectiveness of the early culture in interdicting the fast-growing Gram negative bacteria. The decrease over time in reported sepsis and related fatalities from platelet transfusion, and in the proportion of such fatalities attributed to Gram negative bacteria, is supported by the transfusion-related fatality reports submitted to FDA (Refs. 31 and 32).

The early culture false negative result is believed to be due to the presence of a very small bacterial load at the time of sampling, resulting in a sampling error such that no bacterial organisms are present in the sample, while organisms remaining in the apheresis unit continue their proliferation to levels capable of causing bacteremia and potential clinical sepsis. As mentioned earlier, the bacterial load, at sampling time in contaminated units, is estimated to range from less than 0.002 to 0.26 CFU/mL with an average ranging, in different studies, from 0.1 CFU/mL to 0.25 CFU/mL (Refs. 7 and 8). Thus, the recovery of bacteria in a sample is considered a rare event and its occurrence has been modeled by a Poisson probability distribution. The number of bacteria present in a sample is a function of the sampling volume, and of the bacterial concentration in the bag. Detection by culture also depends on the incubation parameters such as the duration of incubation, and the aerobic or anaerobic conditions.

A published Poisson distribution model predicts that an early culture sampling volume of 4 mL, 8 mL, and 16 mL would respectively detect 46 percent, 71 percent, and 91 percent of bacterially contaminated platelet products at a contamination level of 0.154 CFU/mL (Refs. 20 and 22). The caveat is that the Poisson distribution model is a mathematical construct being applied to a biologic process and rests on a number of assumptions that may not consistently and uniformly apply to all apheresis platelet products (Refs. 9, 20, 22). While the detection rates predicted by the Poisson model have been validated in a separate *experimental* seeding study in which low levels of a single bacterial organism were spiked into a platelet product that was subsequently repeatedly sampled and tested for bacterial detection, they are at significant variance with the day 1 early culture *clinical* sensitivity described above (Ref. 33). The discordance has been ascribed by the authors of the Poisson model to differences in platelet

collection, sampling method, sample volume, and culture conditions between the different studies, and by the wide error margins inherent in studying rare events (Ref. 20).

The Poisson probability distribution has also been used to model the residual rate of bacterial contamination based on the *unconfirmed* day 1 positive culture results (a repeat sample having shown a negative result). This approach suggests that unconfirmed positive results serve as an indirect measure of low level dormant bacteria that cannot be repeatedly detected by the early culture (Ref. 34). Based on this model, the authors have estimated that for every confirmed positive apheresis platelet donation detected by the early culture there may be as many as 19 donations contaminated with viable bacteria that remain dormant at the time of sampling but which may proliferate during prolonged platelet storage to clinically significant levels.

b. Pre-storage pooled WBD platelets

Single units of WBD platelets may be pooled and tested ≥ 24 hours after collection, and stored in an FDA-cleared container for extended pool storage for up to 5 days consistent with the container package insert (Refs. 18 and 35). The rate of bacterial contamination in such pre-storage pooled platelets varies from ~ 1/1,000 to ~ 1/2,500 (Refs. 13 and 36). For pre-storage pooled platelets that had tested negative by early culture, the residual risk of bacterial contamination at the time of transfusion ranges between ~ 1/1,000 and ~ 1/6,000 and the calculated sensitivity of early culture of pre-storage pooled platelets varies between 54 percent and 70 percent (Ref. 13).

Thus the residual risk at the time of transfusion of pre-storage pooled platelets appears comparable to that of apheresis platelets when a culture has been conducted early in storage.

c. Post-storage pooled WBD platelets

Single units of WBD platelets may also be stored as single units and pooled within 4 hours prior to transfusion. Such practice is referred to as post-storage pooling. Pools constituted just prior to transfusion from bacterially untested single units prepared by the PRP (platelet-rich plasma) method have been cultured with a bacterial contamination rate estimated at ~ 1/418 (Ref. 37) in one study by sampling 1-2 mL from the *final constituted pool* (the single units having been leukoreduced at collection) onto a

traditional plate culture just prior to transfusion. Another study that has sampled a 7.5-10 mL volume obtained *by pooling samples* drawn from individual leukoreduced single units into an automated culture method bottle at least 24 hours after collection, showed a contamination rate of 1/5,683 (Ref. 29). The disparity in detection rate between the two studies was most likely related to the difference in product sampling time. In the latter study, sampling occurred early in storage, whereas in the former study sampling was late in storage when bacterial load and bacterial detection are expected to be the highest.

d. Single units of WBD platelets

Individual single units of WBD platelets prepared by the platelet-rich plasma method are typically not cultured; however, using an automated culture system on a 4.5 mL sample taken *at least 24 hours after collection*, a study on 13,579 leukoreduced single units detected one true positive (Ref. 38). A different study on 12,062 leukoreduced single units of WBD platelets tested *between one day and 5 days after collection*, using a different automated culture system that sampled 2-3 mL, resulted in 4 confirmed positive results (~1/3,000) (Ref. 39). As discussed in the preceding paragraph, the disparity in detection rate between the two cited studies was most likely associated with a difference in product sampling time.

3. Risks of sepsis and sepsis-related fatality

Passive hemovigilance reports (initiated by the transfused patient's clinical team after a transfusion reaction is diagnosed) for distributed apheresis platelets that had tested negative by early culture reveals rates approximating 1/100,000 for transfusion-related sepsis (38 septic reactions/4 million apheresis units), and 1/210,000 (1 fatality/210,000 apheresis units) to 1/million (4 fatalities/4 million apheresis units) for sepsis-related fatalities (Refs. 2, 29, 34). Additionally, 42 percent and 53 percent of reported septic reactions occurred with day 4 and day 5 transfusions, respectively, and all related fatalities were evenly split between days 4 and 5 transfusions (Ref. 17).

For pools of WBD platelets prepared by the platelet-rich plasma method and constituted just prior to transfusion, the rate for sepsis by passive hemovigilance reporting is approximately 1/25,000 (Refs. 29 and 36), and that for sepsis-related fatalities is approximately 1/253,504 (Ref. 36). This is in harmony with reported rates of bacterial contamination and of septic transfusion reactions of about 5 times higher in post-storage pooled

platelets than in apheresis platelets (Refs. 40 and 41). This finding is consistent with the average number of five single WBD units combined together to make a pooled product, and the absence of pooling in apheresis platelets.

However, active reporting (based on prospective follow-up on transfused recipients) at a single institution (Ref. 40) has shown a rate of transfusion-associated septic reactions of about 10 times that identified by passive reporting (1/6,400 vs. 1/66,000) indicating that the latter mode of reporting, which is predominant in the U.S., grossly underreports septic transfusion reactions.

B. Non-Culture-Based Rapid Bacterial Detection Devices

1. Rapid testing characteristics

FDA-cleared rapid bacterial detection devices have a rapid turn-around time (typically with a read-out of less than one hour), require a small sampling volume (< 1 mL), and can be used just prior to transfusion. The lower analytical sensitivity (higher limit of detection) of currently available rapid tests compared to culture-based devices dictates their use late in storage when the bacterial load present in the platelet product is expected to be higher than in early storage due to bacterial proliferation.

Consistent with the instructions for use of the FDA-cleared devices, rapid testing of apheresis platelets is conducted within 24 hours prior to transfusion. Testing of post-storage WBD platelet pools is performed within the 4 hours prior to transfusion based on the limitation on the storage period of the pooling storage container.

2. Clinical performance of rapid device

a. Apheresis products

In a clinical field study on apheresis platelets that were screened as negative by early culture, the products were retested with a rapid device on the day of transfusion (Ref. 16). A detection rate of 1/3,069 (0.033 percent) was found for the rapid device, with a concurrent culture test rate of 1/2,302. Thus the rapid device was able to detect contaminated platelet units that were missed by the day 1 culture method. The false positive rate of the rapid device based on a recommended repeat test strategy was 0.51 percent, and it was 0.91 percent based on an initial reactive result only. An

analysis of a subset of the study showed a false negative rate of 0.02 percent and approximate sensitivity and specificity of 60 percent and 99.3 percent, respectively.

In a similar but smaller clinical study, a rapid test on day 4 detected no bacterial contamination in 3,505 apheresis platelets previously screened as negative by the early culture (Ref. 42). The false positive rate was 0.14 percent and 0.71 percent based on repeat and single testing strategy, respectively.

A rapid test with a high false positive rate could lead to the discard of a number of otherwise suitable platelet products, and potentially limit the availability of HLA, or ABO-matched platelets, or of fresh platelets. Platelet inventories in facilities where platelet inventory is low, and transfusions are administered infrequently, would be particularly impacted by a high false positive rate.

Variability in the analytical performance of a rapid test has been described, and it has been linked, in some studies, to a deficiency in its detection technology leading to test sensitivity below the performance stated in the package insert (Refs. 16, 25, 43, 44, 45). Such a decrease in sensitivity resulted in a false negative rapid test result on a clinical product that was ultimately transfused, causing a septic reaction in the recipient (Ref. 16).

Theoretically, a proliferating organism may reach the limit of detection of the device minutes or hours after the test is performed. The relative safety period following a negative rapid test depends on many factors, including the sensitivity of the test, the species and particular strain of the proliferating organism, the bacterial load at sampling time, the clinically significant increase in bacterial proliferation during product storage following a negative test result, and the status of the patient. Testing at a time most proximate to transfusion would be expected to increase product safety.

Nevertheless, bacterial growth kinetics and outcomes of current culture-based testing strategies favor a rationale for a 24-hour relative safety period following a negative rapid test result. As stated previously, day 1 cultures have been relatively effective in interdicting the fast-growing more pathogenic bacterial organisms. The residual risk later in storage has been mostly associated with slow growing organisms, or organisms with an extended lag phase that may be less likely to be clinically relevant. Fast-growing organisms that were missed by the early culture due to sampling

error would have proliferated, by day 4 or day 5, to titers that are unlikely to fall below the limit of detection of a rapid test performed on those days (Refs. 20 and 22). Slow-growing organisms, while potentially undetectable by day 4 or day 5 rapid testing, are unlikely to proliferate to levels that would be detectable shortly after the performance of the test precisely because of their growth kinetics and prolonged doubling time.

Transfusion of platelets within 24 hours of a negative test entails testing of the product no more than once a day, thereby limiting the number of entries through sterile docking and the opportunities for contamination from product entry, as well as minimizing product loss.

b. Post-storage pooled WBD platelets

In a U.S. study, 70,561 non-leukoreduced post-storage WBD platelet pools were tested with a rapid test (Ref. 46). The overall contamination rate was 1:10,080 (0.01 percent), and the false-positive rate was 1:292 (0.34 percent) for a false positive/true positive ratio of 34. The contamination rate in this study was approximately 3 times lower than that encountered in a study described above using the same rapid test but on culture-negative apheresis platelets (Ref. 16). It was also 25 times lower than that detected in a similar, but leukoreduced WBD pooled platelet product (Ref. 46). This discrepancy in detection rate has been ascribed to the ability of leukocytes, in non-leukoreduced platelet products, to phagocytize bacteria (Ref. 47).

IV. PUBLIC MEETINGS ON THE ISSUE OF BACTERIAL CONTAMINATION OF PLATELETS

In 2012, two public meetings were held to discuss the issue of bacterial contamination of platelets. AABB sponsored a workshop on secondary testing of platelets in July 2012, and the FDA Blood Products Advisory Committee (BPAC or Committee) discussed the issue in September 2012 (Ref. 10).

During these public meetings, a number of transfusion services expressed reservations as to the implementation of rapid testing of platelet components prior to their transfusion. Logistical challenges and cost issues were cited as hurdles to the implementation of a strategy intended to prevent rare adverse events. It was noted that rapid devices have a relatively high false positive rate that may lead to the discard of otherwise suitable products thereby compromising platelet availability. Concerns were expressed that the false positive rates could disproportionally impact hospitals with limited platelet inventory that annually transfuse a small number of platelets. In

these small hospitals a false positive result on a product dedicated to a specific patient (such as an HLA-matched or ABO compatible product) could result in a significant delay of a needed platelet transfusion. Additionally, the challenges of implementation of rapid testing in a fixed resource environment were believed to lead to an increase of risks by creating constraints elsewhere in the hospital laboratory and blood bank. Other transfusion services reported on the feasibility and successful implementation of rapid testing on pools of WBD platelets, noting that only a small proportion of units had to be released before completion of the testing because of clinical urgency (Ref. 46). Compared to testing with a pH indicator (a surrogate marker for the presence of bacteria widely used prior to the advent of rapid testing), the adoption of rapid testing has led to a reduction in the number of platelet units that were discarded due to false positive results (Ref. 46).

BPAC recommended that additional measures be taken to decrease the risk of transfusing contaminated platelets, recommended against a reduction in dating to four days, and voted for instituting rapid testing on day 4 and day 5 platelets following the performance of an early culture. The Committee did not formally discuss or vote on FDA's proposal to extend dating to 7 days based on additional bacterial testing. However, some Committee members expressed concern about the quality of 7-day platelets and remarked that platelet efficacy decreases with length of storage. FDA indicated that 7-day apheresis platelet containers have been previously cleared by the Agency based on the same criteria applied to 5-day platelets; hence, there was no compromise in the minimum efficacy standards applied to the extension of platelets to 7 days (Ref. 10).

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